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6. AUTHOR(S) Pablo G. Debenedetti			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Princeton University Department of Chemical Engineering Princeton, NJ 08544-5263			**8. PERFORMING ORGANIZATION REPORT NUMBER**
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13. ABSTRACT (Maximum 200 words)

The principal objective of this research is to improve basic understanding of the deposit of pyrolytic products from thermally-stressed endothermic fuels. The precipitation of picene from supercritical methylcyclohexane was investigated numerically. The calculations indicated that a negligible amount of deposits were formed as a result of friction-driven depressurization in tubular flow. However, the presence of small amounts of particulate impurities dramatically enhanced the rate of deposit formation. Mathematical models were also developed for mass transfer between droplets and a partially-miscible supercritical solvent, and for particle formation during the rapid expansion of supercritical solutions. The evolution of isolated droplets exposed to a supercritical solvent was investigated at mixture sub-critical pressures. Over a wide range of conditions the calculations showed appreciable initial droplet swelling, followed by evaporation. Aerosol dynamics equations were combined with mass, momentum, energy balances and an equation of state to yield a mathematical model for the evolution of the particle size during steady, one-dimensional friction-driven expansions of a supercritical fluid containing a dissolved solute. The calculations showed that only sub-micron particles are formed inside the tube where choked flow conditions are attained. Inter-particle coagulation in the free-jet following the expansion device is responsible for subsequent particle growth.

14. SUBJECT TERMS Nucleation; pyrolytic deposits; supercritical fuels; deposit formation; supercritical antisolvents			**15. NUMBER OF PAGES** 13
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1. OBJECTIVES

The principal objective of this project was to investigate theoretically and computationally the deposit of pyrolytic products from supercritical fuels. In addition, mathematical models of particle formation during the rapid expansion of supercritical solutions, and of mass transfer between droplets and supercritical solvents were formulated and studied numerically. The production of biologically-active protein powders using supercritical fluids was studied experimentally.

2. MAIN FINDINGS

2.1 Deposition of Pyrolytic Products from Thermally-Stressed Supercritical Fuels

The physical processes that give rise to the deposition of pyrolytic products from thermally stressed endothermic fuels formation (nucleation, condensation, coagulation) influence the overall deposition rate in very different ways. This is illustrated in Figure 1, which shows the calculated deposition rate of picene (deposit) from supercritical methylcyclohexane (fuel) as a result of depressurization during flow. Although substantial deposition is predicted under thermodynamic control (instantaneous precipitation; mixture is always at its equilibrium composition), the actual rates resulting from nucleation and condensation are orders of magnitude lower, suggesting that a negligible amount of deposits is formed as a result of friction-driven depressurization in tubular flow.

The presence of small amounts of entrained microparticulates (seeds) can have a very pronounced effect in increasing the deposition rate. This is illustrated in Figure 2, also for the system picene-methylcyclohexane. In this figure, 10^{10} seeds/cc correspond to 1, 10, and 1000 ppm, respectively, for the three seed diameters shown. It follows that the presence of very small amounts of entrained impurities can adversely affect the performance of thermally stressed endothermic fuels.

2.2 Particle Formation During the Rapid Expansion of Supercritical Solutions (RESS)

The first complete model of particle formation during the expansion of supercritical solutions has been formulated and solved numerically (Weber et al., 1999). The model addresses the formation of particles as a result of nucleation, condensation, and interparticle coagulation during steady, one-dimensional flow of supercritical fluids containing dissolved non-volatile solutes. It consists of mass, momentum, and energy balances, coupled to an aerosol dynamics model.

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Typical model calculations are shown in Figure 3. The phenanthrene particle size distributions resulting from the rapid expansion of a saturated mixture of phenanthrene in supercritical carbon dioxide are shown at various locations along a capillary. The calculations give the evolution of the particle size distribution along the axis of the expansion device. The driving force for the formation of particles is pressure drop caused by friction. This, in turn, leads to a decrease in the density of the solvent, and hence to loss of solvent power. In order to obtain the detailed information about particle size distributions shown in the figure, it is necessary to incorporate nucleation, condensation, and coagulation into the aerosol dynamics calculations.

Numerical solution of the model over a wide range of supercritical temperatures and pressures, and of capillary length-to-diameter ratios, yielded particle sizes always smaller than 1 μm. Inter-particle coagulation in the free-jet expansion beyond the capillary's exit, a region not included in the present model (Weber et al., 1999) is therefore a key mechanism leading to the formation of the experimentally-observed particles in the 10-50 μm size range.

2.3 Behavior of Droplets in a Partially Miscible Supercritical Fluid

An important method for forming microparticles, known as the supercritical anti-solvent process (SAS), involves contacting droplets of an organic solvent with a dissolved solute. If a supercritical fluid having appreciable mutual solubility with the solvent, but poor solvent power towards the dissolved solute is contacted with the organic solution, two-way mass transfer of the supercritical fluid into the droplet, and of the organic solvent into the supercritical fluid, occurs. This leads eventually to solute precipitation. This technique has been used to make a variety of microparticulate solid phases, including protein powders, polymer fibers, and polymer spheres, with potential applications ranging from direct delivery of aerosolized drugs to the lungs to formation of engineering plastics with improved mechanical properties (Eckert et al., 1996).

A model of two-way mass transfer has been formulated and solved numerically (Werling and Debenedetti, 1999). Figure 4 illustrates the evolution of 50 μm toluene droplets in supercritical carbon dioxide at 82.5 bar. The arrows show the time it takes for the droplet to attain maximum swelling, and to achieve saturation at its center, respectively. The temperature dependence of these two lifetime measures is shown in the inset. Note the non-monotonic dependence of the time to saturation upon bulk temperature. Note also the appreciable droplet swelling, which is due to the sensitivity of the liquid-phase density to composition in the vicinity of the mixture's critical locus. As long as the equilibrium mixture at the interface is below its critical pressure, droplets were always found to swell appreciably before evaporating.

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These calculations represent the first step towards the formulation of an engineering model of the SAS process. They are being supplemented with a nucleation model and an energy balance (ongoing work). This will allow the calculation of time-dependent particle size distributions under non-isothermal conditions.

2.4 Production of Biologically-Active Protein Powders

We have used the SAS technique to produce microparticulate powders of insulin, lysozyme, and trypsin in the 2-4 μm size range. The proteins retain their biological activity upon re-dissolution in water. This type of powders is potentially useful for direct aerosolized delivery to the lungs, and for incorporation into polymeric drug delivery matrices (Winters et al., 1996).

The powders produced by the anti-solvent technique retain their structural integrity during long-term storage (> 1 yr) and recover their biological activity upon redissolution in water following prolonged dry storage. High-temperature (60°C) storage during three days revealed no changes in secondary structure. These results demonstrate that long-term storage of non-native protein structures does not result in loss of stability or biological activity, and suggest that SAS processing may be a useful finishing step in protein processing for therapeutic applications (Winters et al., 1997).

Supercritical carbon dioxide was used as an antisolvent to induce the semi-batch precipitation of proteins from organic solution. Because each protein has a distinct precipitation pressure, this technique can be used to fractionate mixtures of proteins. We tested this idea experimentally and found that, indeed, the use of supercritical carbon dioxide is a very convenient and effective route for fractionating protein mixtures. Insulin, lysozyme, ribonuclease, and trypsin precipitates obtained from dimethyl sulfoxide solutions pressurized with supercritical carbon dioxide recovered substantial amounts of biological activity upon redissolution in water. Alkaline phosphatase, however, was irreversibly denatured (Winters et al., 1999).

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3. PERSONNEL

3.1 Supported
Michael Winters; graduate student
Jane Werling; graduate student
Srikanth Sastry; post-doctoral associate
Pablo G. Debenedetti; principal investigator

3.2 Other Collaborators
Dr. Markus Weber; post-doctoral associate, supported by the Swiss National Science Foundation

4. PUBLICATIONS DESCRIBING AFOSR-SPONSORED RESEARCH, 5/1/96 - 4/30/99

4.1 Published or in Press
M.A. Winters, B.L. Knutson, P.G. Debenedetti, H.G. Sparks, T.M. Przybycien, C.L. Stevenson, and S.J. Prestrelski, "Precipitation of Proteins in Supercritical Carbon Dioxide," **J. Pharm. Sci., 85**, 586 (1996).

H. Inomata, S. Saito, and P.G. Debenedetti, "Molecular Dynamics Simulation of Infinitely Dilute Solutions of Benzene in Supercritical CO2," **Fluid Phase Equil., 116**, 282 (1996).

M.A. Winters, P.G. Debenedetti, P.D. Condo, M. Radosz, and H.-W. Schmidt, "Effects of Compressed Carbon Dioxide on the Phase Equilibrium and Molecular Order of a Lyotropic Polyamide Solution," **Macromolecules, 29**, 4904 (1996).

B.L. Knutson, P.G. Debenedetti, and J.W. Tom, "Preparation of Microparticulates Using Supercritical Fluids," in *Microparticulate Systems for the Delivery of Proteins and Vaccines*, S. Cohen and H. Bernstein, eds., ch. 3, Marcel Dekker, New York, 1996.

C.A. Eckert, B.L. Knutson, and P.G. Debenedetti, "Supercritical Fluids as Solvents for Chemical and Materials Processing," **Nature, 383**, 313 (1996).

M.A. Winters, P.G. Debenedetti, J. Carey, H.G. Sparks, S.U. Sane, and T.M. Przybycien, "Long-Term and High-Temperature Storage of Supercritically-Processed Microparticulate Protein Powders," **Pharm. Res., 14**, 1370 (1997).

M.A. Winters, D.Z. Frankel, P.G. Debenedetti, J. Carey, M. Devaney, and T.M. Przybycien, "Protein Purification with Vapor-Phase Carbon Dioxide," **Biotech. & Bioeng., 62**, 247 (1999).

J. Werling and P.G. Debenedetti, "Numerical Modeling of Mass Transfer in the Supercritical Antisolvent Process," **J. Supercrit. Fluids,** in press (1999).

4.2 In Preparation
M. Weber, L.M. Russell, and P.G. Debenedetti, "Mathematical Modeling of Particle Formation During the Rapid Expansion of Supercritical Solutions (RESS)", to be submitted to **J. Supercrit. Fluids**.

5. TECHNICAL PRESENTATIONS DESCRIBING AFOSR-SPONSORED RESEARCH, 5/1/96 - 4/30/99

"Theoretical and Computational Studies of Nucleation in Supercritical Fuels." AFOSR Contractors Meeting, Virginia Beach, Virginia, June 4, 1996.

"Particle Formation from Supercritical Fluids." International Fine Particle Research Institute Annual Meeting, Nancy, France, June 11, 1996.

"Materials Processing with Supercritical Fluids." Third International Symposium on High Pressure Chemical Engineering, ETH (Swiss Federal Institute of Technology), Zürich, Switzerland, October 8, 1996.

"Materials Processing with Supercritical Fluids." David Sarnoff Research Center, Princeton, December 4, 1996.

"Materials Processing with Supercritical Fluids." Bristol-Myers Squibb, New Brunswick, NJ, January 3, 1997.

"Materials Processing with Supercritical Fluids." Inhale Therapeutic Systems, Palo Alto, CA, May 21, 1997.

"Materials Processing with Supercritical Fluids." Engineering Foundation Conference on Separation Technology: Separations for Clean Production, Davos, Switzerland, October 28, 1997.

"Phase Separation by Nucleation and Growth, and by Spinodal Decomposition: Fundamentals." NATO Advanced Study Institute, Supercritical Fluids. Fundamentals and Applications, Kemer, Turkey, July 20, 1998.
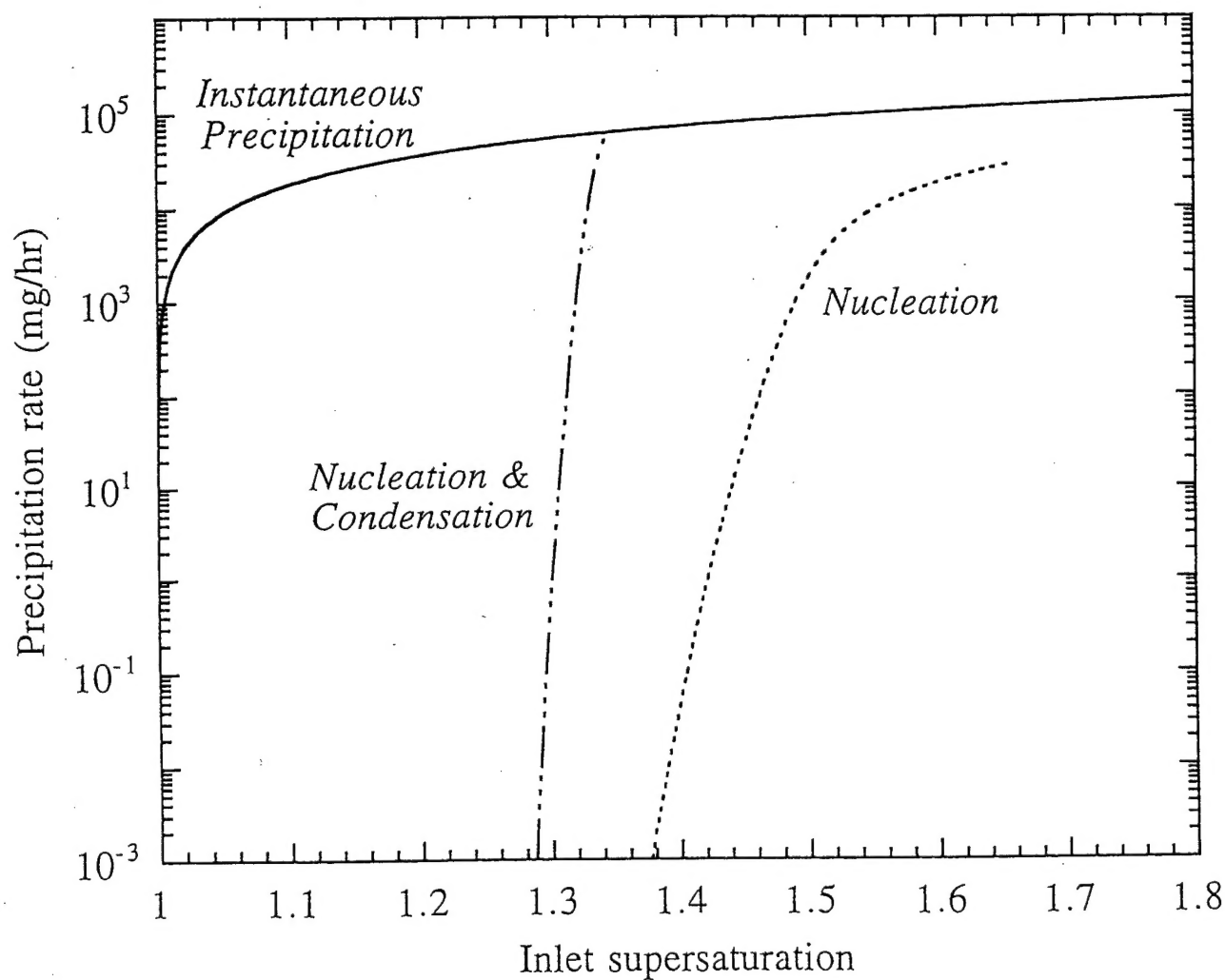
Figure 1: Calculated rate of picene deposition from supercritical methylcyclohexane (MCH), flowing at a rate of 13 kg/hr inside 2 mm i.d. tubing. The deposition rate has been integrated along 10 cm of tubing. Inlet conditions are 620 K and 70 bar. The x-axis gives the ratio of actual to equilibrium picene mole fraction at the entrance. Instantaneous precipitation conditions correspond to a mixture that is always saturated along the tube.
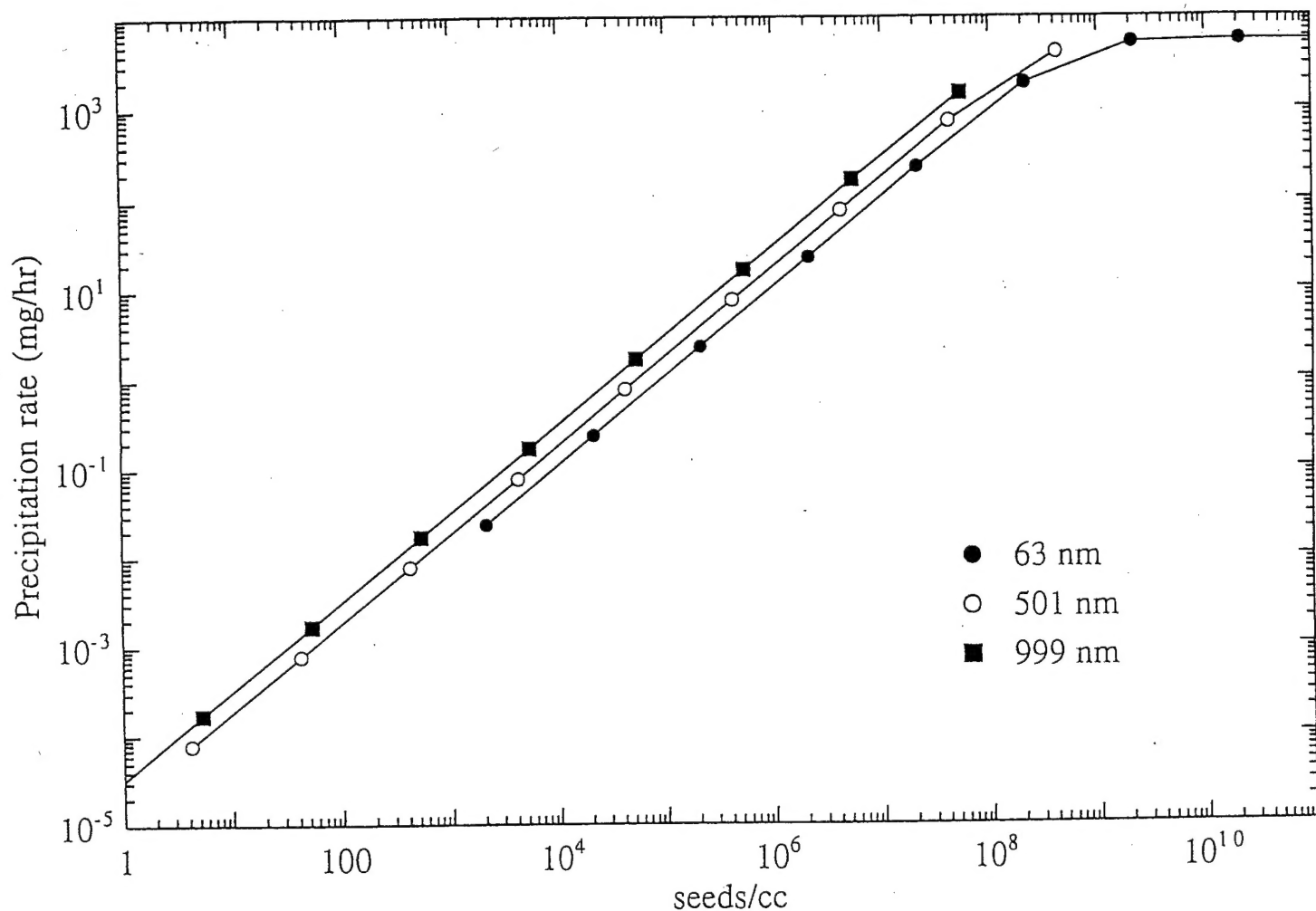
Figure 2: Calculated rate of picene deposition from supercritical methylcyclohexane in the presence of entrained microparticulates (seeds). Other conditions are the same as shown in Figure 1, with saturated conditions at the entrance. The figure illustrates the dramatic enhancements in deposition rates that can result from the presence of entrained microparticulates.
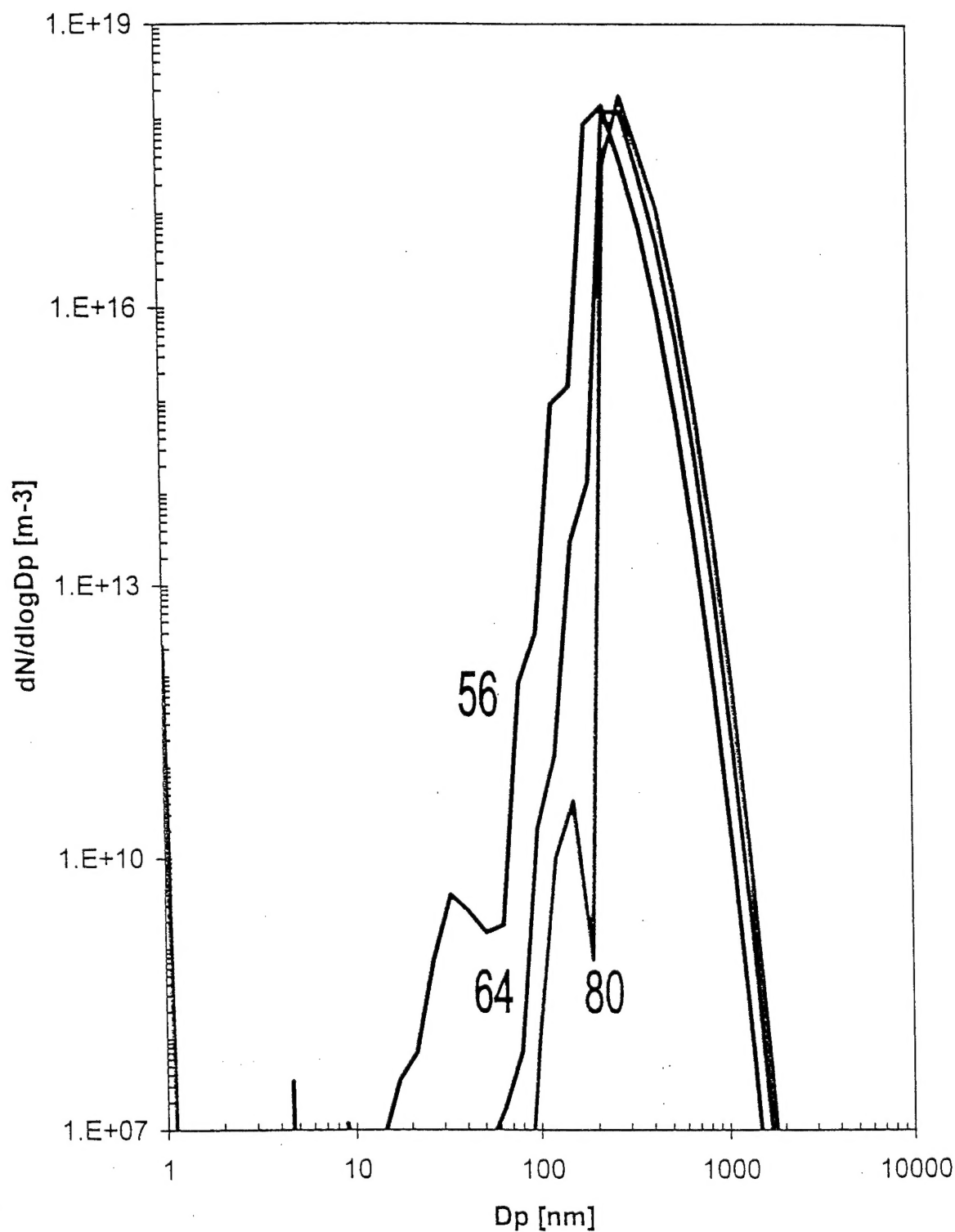
Figure 3: Phenanthrene particle size distributions (number density) at three positions inside a 100 μm i.d., 100 mm L capillary during the steady, friction-driven expansion of a saturated mixture of phenanthrene in supercritical carbon dioxide. The labels on the curve denote axial locations in mm. The inlet conditions are 343 K and 200 bar, and the flow is choked at the capillary's exit (Weber et al., 1999).
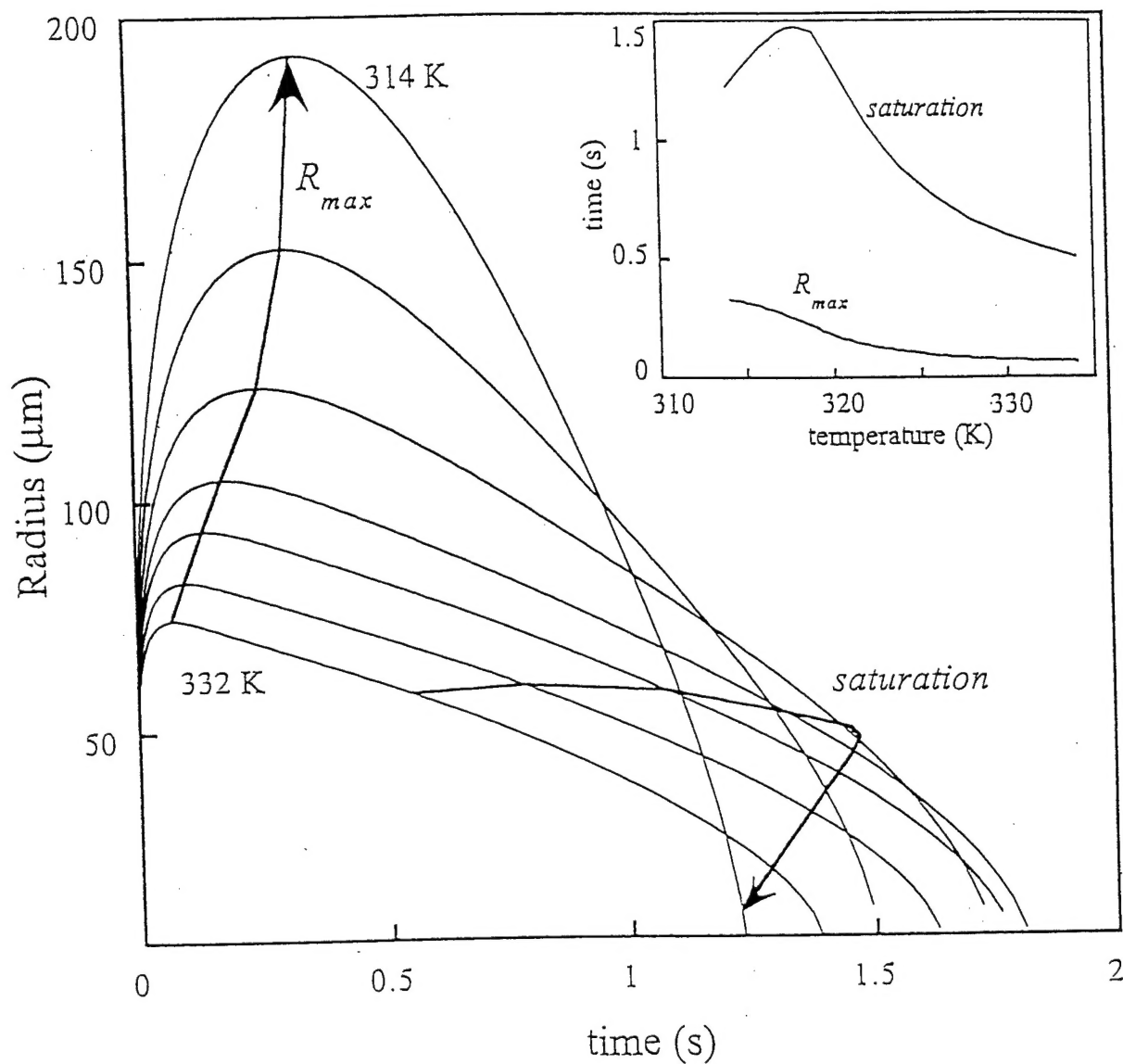
Figure 4: Evolution of 50 μm toluene droplets exposed to supercritical carbon dioxide at 82.5 bar over a range of supercritical temperatures. Note the appreciable initial swelling, which was always found to occur whenever the equilibrium mixture at the interface was below its critical pressure. The inset shows the temperature dependence of the time it takes for the droplet to attain its maximum size, and for the droplet to become saturated with carbon dioxide at its center. (Werling and Debenedetti, 1999).

Principal Investigator Annual Data Collection (PIADC) Survey Form

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PI DATA

Name (Last, First, MI): Debenedetti, Pablo G.

Institution: Princeton University

Contract/Grant No. F49620-96-1-0169

NUMBER OF CONTRACT/GRANT CO-INVESTIGATORS

Faculty __1__   Post Doctorates __2__   Graduate Students __2__   Other_____

PUBLICATIONS RELATED TO AFOREMENTIONED CONTRACT/GRANT

NOTE: List names in the following format: Last Name, First Name, MI

Include: Articles in peer reviewed publications, journals, book chapters, and editorships of books.

Do Not Include: Unreviewed proceedings and reports, abstracts, "Scientific American" type articles, or articles that are not primary reports of new data, and articles submitted or accepted for publication, but with a publication date outside the stated time frame.

Name of Journal, Book, etc.: Journal of Pharmaceutical Science

Title of Article: Precipitation of Proteins in Supercritical Carbon Dioxide

Author(s): Winters, M.A.; Knutson, B.L.; Debenedetti, P.G.; Sparks, H.G.; Przybycien, T.M.; Stevenson, C.L.

Publisher (if applicable): _____

Volume: 85   Page(s): 586-594   Month Published: June   Year Published: 1996

Name of Journal, Book, etc.: Fluid Phase Equilibria

Title of Article: Molecular Dynamics Simulation of Infinitely Dilute Solutions of Benzene in Supercritical CO_2

Author(s): Inomata, H.; Saito, S.; Debenedetti, P.G.

Publisher (if applicable): _____

Volume: 116   Page(s): 282-288   Month Published: _____   Year Published: 1996

Name of Journal, Book, etc.: Macromolecules
Title of Article: Effects of Compressed Carbon Dioxide on the Phase Equilibrium and
Molecular Order of a Lyotropic Polyamide Solution
Author(s): Winters, M.A.; Debenedetti, P.G.; Condo, P.D.; Radosz, M.; Schmidt, H.-W.
Publisher (if applicable):
Volume: 29   Page(s): 4904-4909 Month Published: Year Published: 1996

Name of Journal, Book, etc.: Microparticulate Systems for the Delivery of Proteins and
Vaccines
Title of Article: Preparation of Microparticulates Using Supercritical Fluids
Author(s): Knutson, B.L.; Debenedetti, P.G.; Tom, J.W.
Publisher (if applicable): Marcel Dekker, Inc.
Volume: Page(s): 89-125   Month Published: Year Published: 1996

Name of Journal, Book, etc.: Nature
Title of Article: Supercritical Fluids as Solvents for Chemical and Materials Processing
Author(s): Eckert, C.A.; Knutson, B.L.; Debenedetti, P.G.
Publisher (if applicable):
Volume: 383 Page(s): 313-318   Month Published: Sept.   Year Published: 1996

Name of Journal, Book, etc.: Pharmaceutical Research
Title of Article: Long-Term and High-Temperature Storage of Supercritically-Processed
Microparticulate Protein Powders
Author(s): Winters, M.A.; Debenedetti, P.G.; Carey, J.; Sparks, H.G.; Sane, S.;
Przybycien, T.M.
Publisher (if applicable):
Volume: 14   Page(s): 1370-1378 Month Published: Year Published: 1997

Name of Journal, Book, etc.: Biotechnology and Bioengineering
Title of Article: Protein Purification with Vapor-Phase Carbon Dioxide
Author(s): Winters, M.A.; Frankel, D.Z.; Debenedetti, P.G.; Carey, J.; Devaney, M.;
Przybycien, T.M.
Publisher (if applicable):
Volume: 62   Page(s): 247-258   Month Published: Year Published: 1999

Name of Journal, Book, etc.: Journal of Supercritical Fluids
Title of Article: Numerical Modeling of Mass Transfer in the Supercritical Antisolvent
Process
Author(s): Werling, J.; Debenedetti, P.G.
Publisher (if applicable):
Volume: Page(s):   Month Published: in press Year Published: 1999

HONORS/AWARDS RECEIVED DURING CONTRACT/GRANT LIFETIME

Include: All honors and awards received during the lifetime of the contract or grant, and any life achievement honors such as (Nobel prize, honorary doctorates, and society fellowships) prior to this contract or grant.

Do Not Include: Honors and awards unrelated to the scientific field covered by the contract/grant.

Honor/Awards: Guggenheim Fellow   Year Received: 1991

Honor/Award Recipient(s): Pablo G. Debenedetti

Awarding Organization: John Simon Guggenheim Memorial Foundation

Honor/Awards: Best Professional Book in
                       Chemistry "Metastable Liquids"   Year Received: 1996

Honor/Award Recipient(s): Princeton University Press

Awarding Organization: Association of American Publishers, Inc.

Honor/Awards: Professional Progress Award   Year Received: 1997

Honor/Award Recipient(s): Pablo G. Debenedetti

Awarding Organization: American Institute of Chemical Engineers